IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Houghton et al.	
Application No.: 09/996,128	Group Art Unit: 1642
Filed: 11/27/2001	Examiner: A Harris
Title: Compositions for Treatment of Melanoma and Method of Using Same	Confirmation No: 3698
Attorney Docket No.: MSK.P-026-3	
Customer No.: 52334	

DECLARATION UNDER RULE 132

I, Alan N. Houghton, declare as follows:

1. I am a named inventor of the above-referenced application. As such, I am familiar with the application, including the claims.

2. I understand that in the office action mailed December 27, 2006, the Examiner has cited Zhai et al., *J. Immunol.* 156: 700-710 (1996) as "teaching a method of inducing specific T cell immunity for mammalian metastatic melanoma."

3. The Zhai reference performs tests using B16 melanoma. B16 melanoma is not per se metastatic, and the parental B16 melanoma cells rarely metastasize. Classic experiments with B16 are described in the attached paper (1978). An important point about metastasis is that this represents multiple steps: motility and invasion of cancer cells into tissues, access into bloodstream or lymphatic vessels, spread through vessels to distant sites, migration out of blood vessels and survival in a distant, generally inhospitable tissue. This last point is underappreciated. If you inject 5 million B16 melanoma cells into the bloodstream from the parental B16 melanoma tumor, you will rarely get

metastases (the cells do not survive as lung metastasis, even though large numbers are trapped in the lung capillaries).

4. The Zhai paper only reports B16 melanoma, and do not described in metastatic version. In their experiments, B16 tumor cells are implanted in the skin, and the investigators look for local tumor growth. So-called metastases experiments typically use intravenous injection of tumor cells and look at colonization of organs (e.g., lung). Even these metastases models do not recapitulate all the events for metastases, e.g., tissue invasion and movement into vessels for dissemination. For these reasons, purists call these organ colonization experiments, not metastases experiments. Neither is disclosed in the Zhai reference, and thus there is no showing of relevance to metastatic melanoma.

5. B16 melanoma is not a viable model for canine malignant melanoma (CMM). In addition to not being metastatic, B16 is a single tumor line which spontaneously arose in a mouse ~50 years ago, and happens to grow well when transplanted into syngeneic (e.g. twin) mice. It almost certainly did not arise from the epidermis or mucosa, but rather from melanocytes in hair follicles since C57BL/6 mice do not have melanocytes in the epidermis or mucosa. In contrast, in dogs and humans, melanomas do arise from the epidermis and mucosa. In dogs, aggressive melanoma (CMM) arises from mucosal sites. B16 mouse models do not recapitulate the natural steps in pathogenesis of melanoma in dogs or humans. Moreover, chemotherapeutic drugs which are active against B16 melanoma (e.g., Stephens Br J Cancer 45:821-829, 1982; Stephens & Peacock Br J Cancer 38:591-598, 1978) are inactive in the treatment of melanoma (Houghton et al., Cancer Treat Rep 65: 170-171, 1981; Amrein, Am J Clin Oncol 7: 269-71, 1984.)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

dated: 2-21-2007

Alan N. Houghton